

**REMARKS**

***Specification Amendment***

The paragraph of the specification at page 28, lines 5-16, has been amended to correct what appears to be a misspelling (or a less preferred spelling) of the word “tetratocarcinoma” to –teratocarcinoma--. The basis and reason for this amendment is explained further below.

***Claim Status***

No amendments are made to the claims herein. The claims are presented above for convenience of reference, and incorporate all of the amendments previously made in this application.

Claims 7-9, 13 and 18-22 are presently pending in this application. Claims 7-9, 13 and 18-21 are allowed, and only claim 22 currently stands rejected.

***Claim Rejections – 35 USC § 112***

Claim 22 is rejected under 35 U.S.C. 112, first and second paragraphs, as failing to comply with the written description requirement, and as being vague and indefinite. Specifically, the Examiner asserts that the medical condition “teratocarcinoma” in the list of diseases or medical conditions of claim 22 is not described in the specification, and is vague and indefinite in that it is not known what is meant by the medical condition teratocarcinoma. These grounds for rejection are believed to have been overcome by the above amendment to the specification and the following considerations.

Method claims 18-22 were added by the Amendment filed October 15, 2002, and support for these claims is discussed in the Remarks portion of that Amendment at pages 24-

26, including support from page 28 of the specification. While trying to figure out the basis for this rejection by the Examiner, the undersigned noted that the specification at page 28, line 15, recited “tetratocarcinoma” rather than “teratocarcinoma” as recited in claim 22, and it is understood that this difference in spelling is the basis for this ground for rejection. On further investigation, it is believed that the “tetratocarcinoma” spelling originated from text at page 10 of European Patent Application EP 696593, which is discussed in the present specification at page 2, lines 3-6. While this spelling has been carried through to a small number of patent and literature references, by far the predominant spelling in the patent and published literature is “teratocarcinoma,” which was used in claim 22. In fact, the terms appear to be used interchangeably in an abstract from the journal “Cancer Research,” a copy of which is attached. Moreover, Stedman’s Medical Dictionary defines the term “teratocarcinoma” (a copy of which is also attached), but does not define the term “tetratocarcinoma.” Accordingly, it is believed that the spelling in claim 22 is preferred, and the specification at page 28 has been corrected accordingly.

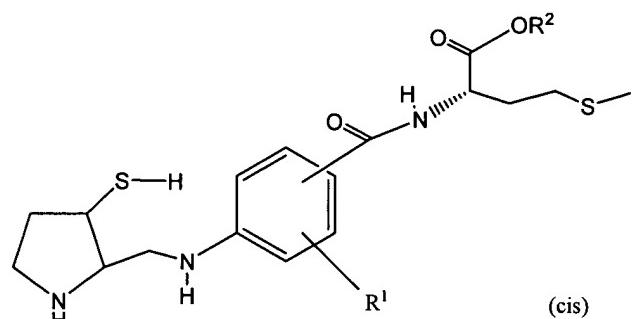
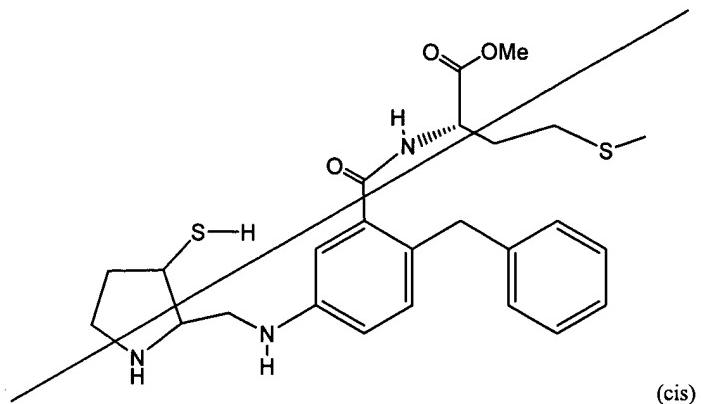
This ground for rejection of claim 22 is therefore believed to have been overcome.

*Specification*

The Amendment filed February 17, 1999 is objected to as introducing new matter into the disclosure. Specifically, the Examiner points to the amended structure on page 64, line 1, and requests that applicants provide clear support for the amendment to the structure.

For convenience of reference, the February 17, 1999 amendment to the specification at page 64 is depicted below, using the redline/strikeout format mandated by the rules in effect today:

Example 12



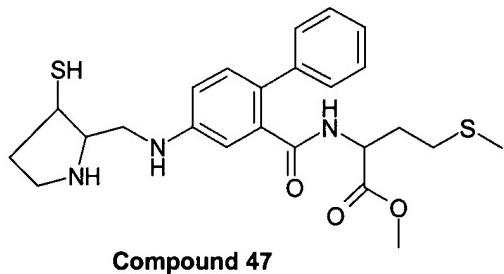
Compound	R <sup>1</sup>	Position of R <sup>1</sup> on phenyl	R <sup>2</sup>	Position of R <sup>2</sup> <u>containing</u> <u>substituent on</u> phenyl
47	Ph-	4	Me	3
48	PhCH <sub>2</sub> -	4	Me	3
49	PhCH <sub>2</sub> CH <sub>2</sub> -	4	Me	3
50	4-F-PhCH <sub>2</sub> CH <sub>2</sub>	3	Me	4
51	PhCH <sub>2</sub> CH <sub>2</sub> -	4	H	3
52	4-F-PhCH <sub>2</sub> CH <sub>2</sub> -	3	H	4

This ground for rejection is respectfully traversed, since both the existence of the error in the original structure of Example 12, and the nature of the needed correction, would have been readily discernable to persons skilled in this art for the reasons detailed below.

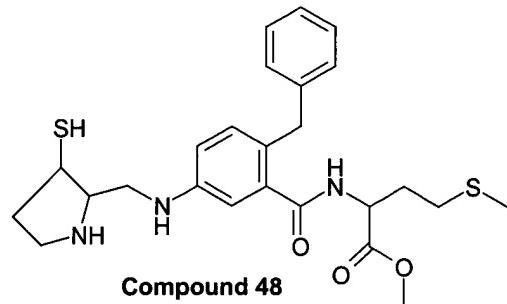
First of all, it would be immediately apparent to a skilled person that the original structure of Example 12 at the top of page 64 is in error, since it depicts a specific compound, whereas the related table that follows refers to a generic structure having variables R<sup>1</sup> and R<sup>2</sup>, and their respective positions on the phenyl ring.

To reconcile this clearly apparent discrepancy between the table and actual structure shown, the skilled person would naturally seek to determine what the generic structure should be. There are two conceivable approaches by which this may be done using the information provided in Example 12, and both approaches lead to the corrected structure that was submitted by the February 17, 1999 Amendment, which corrected structure was also submitted and accepted during the International phase of this application. These two possible approaches are as follows:

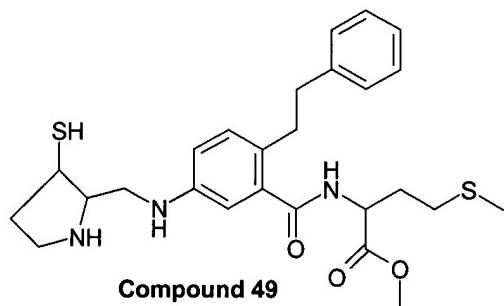
(1) The NMR data for each of compounds 47 though to 52 is set out at page 64, line 11, to page 65, line 30, of the originally filed application. A person skilled in the art will be able to determine the structures of these compounds 47 to 52 using this data. The structures concerned are as follows:



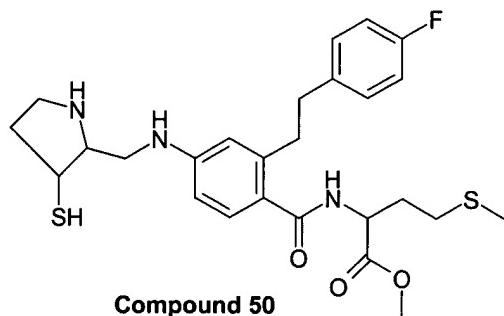
Compound 47



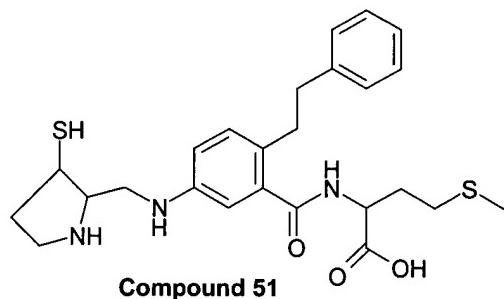
Compound 48



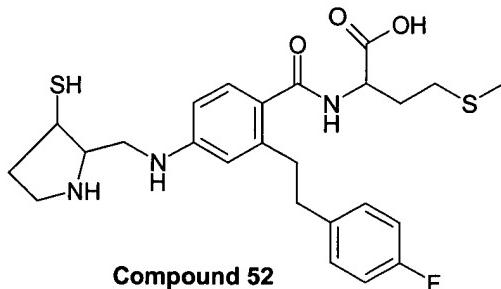
Compound 49



Compound 50



Compound 51



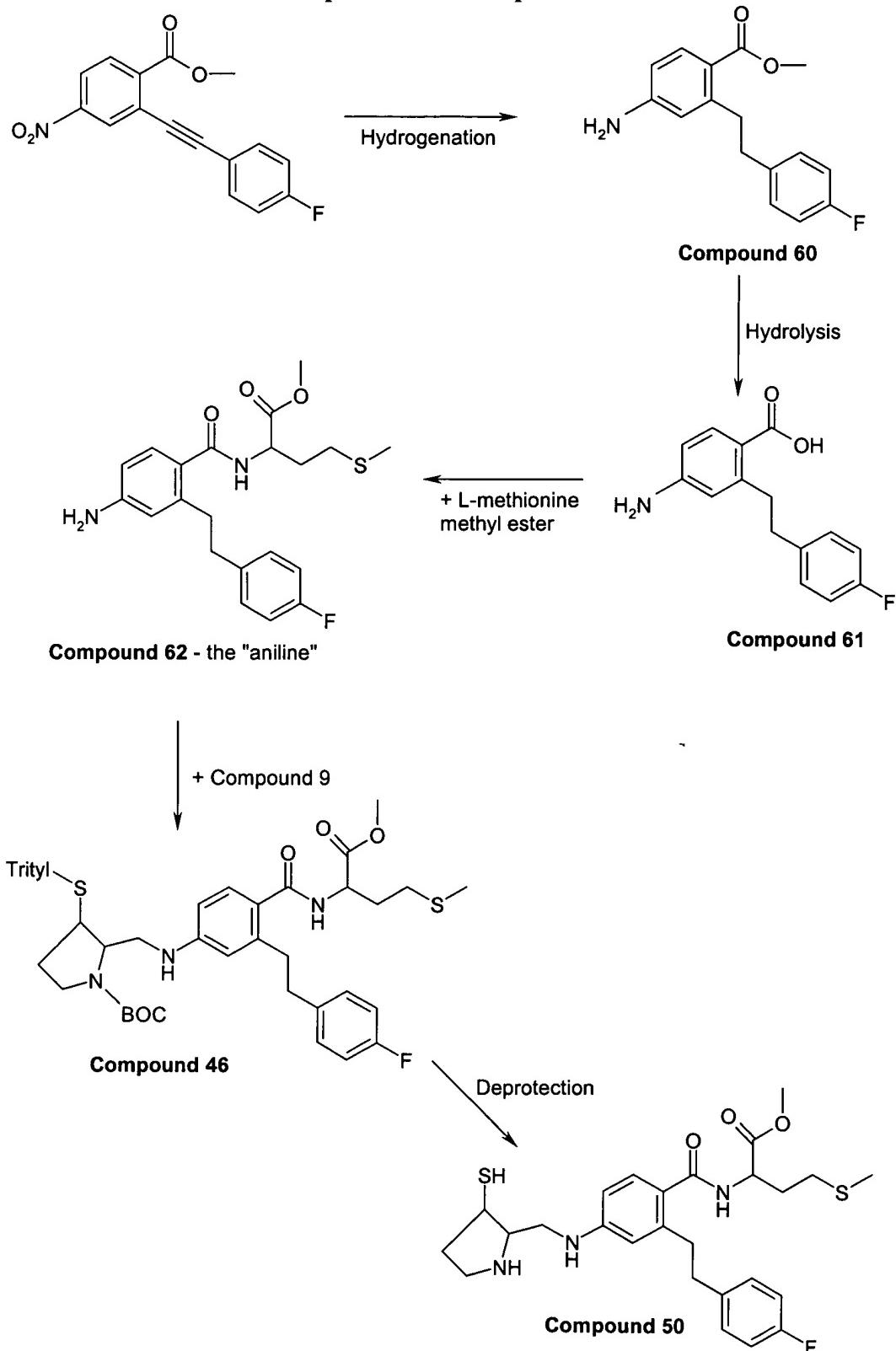
Compound 52

Comparing the structures of these compounds with the information in the table, it is clear what the intended R<sup>1</sup> and R<sup>2</sup> designations should be. This comparison also makes clear that the heading of the last column of the table should read "Position of R<sup>2</sup> containing substituent on phenyl."

(2) This same correct generic structure could also be determined by the skilled person by means of the description of the making of compound 50. Example 12 describes the synthesis of compound 50, which is one of the compounds listed in the table. It is stated at

page 64, lines 8 to 10, that compound 50 was prepared by deprotecting compound 46. At page 66, lines 2 to 3, it is stated that compound 46 is prepared by reacting compound 9 with the "appropriate aniline." The "appropriate aniline" used for preparing compound 46 and its synthesis are described at page 66, lines 21 to 28. Following this synthesis through the specification disclosure provides the reaction scheme shown below. Thus, the actual structure of compound 50 would be readily discernable to a person skilled in this art from the process described for its making in Example 12:

**Preparation of Compound 50**



Comparing this structure with the structure shown in originally filed Example 12, and the information provided in the table below the structure in Example 12, will again leave the skilled person in no doubt that the R<sup>1</sup> group is the 4-fluorophenethyl group of compound 50 and the benzyl group of the structure shown in originally filed Example 12. It is also clear that this group may be in either the 3- or 4- position of the phenyl ring (with the 3-mercaptopyrrolidin-2-ylmethylamino group occupying the 1-position).

In addition, it will also be clear that the R<sup>2</sup> is the methyl ester group. This is apparent from the NMR data, which shows that the methyl ester group of compound 50 is lost when compound 50 is converted to the equivalent acid, compound 52 (in which R<sup>2</sup> = H) as described at page 64, lines 7 to 8.

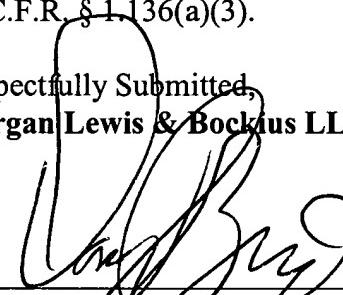
It is therefore respectfully submitted that it would be immediately apparent to a person skilled in the art that the specific structure originally included in Example 12 should instead be a generic structure with the variables R<sup>1</sup> and R<sup>2</sup>, and it would further be apparent to such person, by either approach outlined above, that the generic structure should be the structure that was substituted by the February 17, 1999 Amendment. Since both the existence of the error, and the manner in which it should be corrected would have been readily discernable by the skilled person, the substitution of the correct structure by the February 17, 1999 Amendment does not add new matter to the original disclosure. This ground for rejection should therefore be withdrawn.

### ***Conclusion***

All of the new grounds for rejection have been addressed by the foregoing amendment and remarks, and are believed to have been overcome. Therefore, all claims are now in condition for allowance, and a notice to that effect is respectfully requested.

**EXCEPT** for issue fees payable under 37 C.F.R. § 1.18, the Director is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-0310. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully Submitted,  
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# Cancer Research



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Abstract Deadline: Nov. 30



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## ARTICLES

# Microfluoremetric analysis of DNA content changes in murine teratocarcinoma

DE Swartzendruber, LS Cram and JM Lehman

The multipotential stem cell of the murine teratocarcinoma, embryonal carcinoma (EC), is capable of differentiation in vivo and in vitro to nonneoplastic progeny. Undifferentiated EC cells, spontaneously differentiating teratocarcinoma cells, and differentiated cells derived from EC cells were analyzed for DNA content and chromosome number distributions. Flow microfluorometric and fluorescence cytophotometric analysis of DNA content showed that EC cells had a characteristic diploid (2c) distribution, whereas several differentiated cell lines derived from EC cells had 4c DNA distributions. The tetraploid cell populations studied were capable of cell division but had restricted differentiative potential and were either of low tumorigenicity or non-tumorigenic. In vivo teratocarcinomas, comprised of both EC cells and differentiated cell types, contained diploid and tetraploid populations. Chromosomally, EC cells were neardiploid (39 chromosomes) and differentiated cells were near-tetraploid (62 to 76 chromosomes). The teratocarcinoma provides a model for studying the basic mechanisms that control the growth dynamics of the rapidly and slowly proliferating cell populations present in many tumors.

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24TH EDITION



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teratocarcinoma

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**teratocarcinoma.** 1. A malignant teratoma, occurring most commonly in the testis. 2. A malignant epithelial tumor arising in a teratoma.

**teratogen** (*ter'-a-to-jen*) [ *terato-* + *G. suffix -gen*, producing ]. A drug or other agent that causes abnormal development.

**teratogenesis** (*ter'-a-to-jen'-e-sis*) [ *terato-* + *G. genesis*, origin ]. Teratogeny: the origin or mode of production of a malformed fetus; the disturbed growth processes involved in the production of a malformed fetus.

**teratogenic** (*ter'-a-to-jen'-ik*). Teratogenic.

**teratogenesis**, 2. Causing abnormal development.

**teratopathy** (*ter-a-to-p'ath-i-ah*). Teratogenesis.

**teratoid** (*ter-a-toy'd*) [ *G. teratoides*, fr. *teros* (*terat-*), monster, + *eidos*, resemblance ]. Resembling a *terat-*.

**teratologic** (*ter-a-to-loj'ik*). Relating to teratology.

**teratology** (*ter-a-to-loj'i*) [ *terato-* + *G. logos*, study ]. The branch of science concerned with the production, the development, the anatomy, and the classification of malformed fetuses. See also, dysmorphology.

**teratoma** (*ter-a-to-mah*) [ *terato-* + *G. suffix -oma*, tumor ]. Teratoblastoma: teratoid: tumor; a neoplasm composed of multiple tissues, including tissues not normally found in the organ in which it arises; derivatives of all three germ layers may be found on careful search. It's occur most frequently in the ovary, where they are usually benign and form dermoid cysts; they also occur in the testis, where they are usually malignant, and, uncommonly, in other sites, especially the midline of the body.

**t. orbitae**, orbitopagus.

**trichilemmal t.**, a tumor composed of tissues derived from all three germ layers, i.e., a teratoma.

**teratomatous** (*ter-a-to-ma-tus*). Relating to or of the nature of a teratoma.

**teratophobia** (*ter-a-to-fob'ah*) [ *terato-* + *G. phobos*, fear ]. Morbid fear on the part of a pregnant woman lest she give birth to a malformed fetus.

**teratosis** (*ter-a-to-sis*) [ *terato-* + *G. suffix -osis*, condition ]. Teratism: an anomaly producing a *terat-*.

**anastrephic t.**, one in which any of the normal openings, as the nares, mouth, anus, or vagina, is imperforate.

**ectopic t.**, a malformation in which there is a failure of the lateral halves of a part to unite, as in cleft palate.

**ectopic t.**, one in which there is a deficiency of parts.

**ectopic t.**, one in which the organs or other parts are misplaced.

**hypogenetic t.**, one in which there is a redundancy of parts.

**synaptytic t.**, one in which there is a fusion of normally separated parts.

**teratospermia** (*ter-a-to-sper'mi-ah*) [ *terato-* + *G. sperma*, seed ]. A condition characterized by the presence of malformed spermatozoa in the semen.

**terbium**. [*fr. Ytterby*, a place in Sweden]. A metallic element of the lanthanide or "rare earth" series, symbol *Tb*, atomic no. 65, atomic weight 158.93.

**terbutaline sulfate**,  $\alpha$ -[*(tert-Butylamino)methyl*]-3,5-dibydroxybenzyl alcohol sulfate; a sympathomimetic drug, used principally as a bronchodilator.

**terebene** (*ter'-e-ben*). A thin colorless liquid of an aromatic odor and taste, a mixture of terpene hydrocarbons, chiefly dipentene and terpinene, obtained from oil of turpentine. Used as an expectorant, and in cystitis and urethritis.

**terebinth** (*ter'-e-bin*) [ *G. terebinthos*, the terebinth or terepine-tree ]. The tree, *Pistacia terebinthus* (family, *Pinaceae*), from which Chinese turpentine is obtained; it is native to the shores of the eastern Mediterranean.

**terebinthinate** (*ter'-e-bin-thi-nit*). Terebinthine. 1. Containing or impregnated with turpentine. 2. A preparation containing turpentine.

**terebinthine** (*ter'-e-bin'-thin*). Terebinthinate.

**terebinthism**. Turpentine poisoning.

**terebrant**, **terebrating** (*ter'-e-brant*, -bra-ting) [ *L. terebrare*, *atus* to bore, fr. *terebra*, an auger ]. Boring; piercing; used figuratively, as in the term *t.* pain.

**terebration** (*ter'-e-brash'un*) [ *L. terebra*, to bore, fr. to bore, an auger ]. 1. The act of boring, or of trephining. 2. boring pain.

**teres**, *gen.* teretis, pl. teretes (*ter'-ez*, *ter'-e-tis*, *ter'-e-ti*) [*ter-*] [ *L. round, smooth, fr. terra to rub* ]. Round and long denoting certain muscles and ligaments.

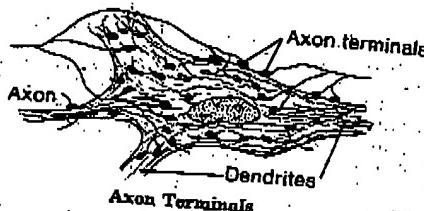
**ter'gum** [ *L. tergum*, back ]. Relating to the back; dorsum [ *L.* ]. Dorsum.

**term** [ *L. terminus*, a limit, an end ]. 1. A definite or limited period. 2. A name or descriptive word or phrase. See also terminus.

**terminad** (*ter'mi-nad*). Toward the terminus.

**terminal** (*ter'mi-nal*) [ *L. terminus*, a boundary, limit ]. 1. Relating to the end; final. 2. Relating to the extremity or end of any body. 3. A termination, extremity, end, or ending.

**axon t's**, end-feet; terminal or axonal terminal boutons; boutons or pieds terminaux; synaptic endings or t's; neuropodia: the somewhat enlarged, often club-shaped endings by which axons make synaptic contacts with other nerve cells or with effector cells (muscle or gland cells). See also synapses.



**synaptic t's**, axon t's.

**terminatio**, pl. **terminations** (*ter'mi-na-shi-oh-nay'shun*) [ *L.*] [ *NA* ]. A termination or ending, particularly a nerve ending. See also ending.

**terminatio'nes nervorum** [*ter'mi-na-shun*], free nerve endings; a form of peripheral coding of sensory nerve fibers in which the terminal filaments end freely in the tissue.

**termination** (*ter'mi-na-shun*) [ *L. terminatio* ]. An end or ending; see terminatio, and ending.

**terminatio'nes** [ *L.* ]. Plural of terminatio.

**termini**, pl. **termini** (*ter'mi-ni-uh-si*) [ *L.* ]. 1. Term, descriptive expression or word. 2. A boundary or limit.

**ter'mini generales** [ *NA* ], general terms; words that are of general use in descriptive anatomy.

**ter'mone** [ *L. ter, thrice, threefold*; + *hormone* ]. A type of ecdysterone, secreted by some invertebrate organisms, that stimulates gametogenesis.

**ter'mary**, [ *L. ternarius* of three ]. Denoting a chemical compound containing three elements, or a complex formed by three molecules.

**ter'oxide**. Trioxide.

**ter'pene**. One of a class of unsaturated hydrocarbons with an empirical formula of  $C_{n}H_{2n}$ , occurring in essential oils and resins. Acyclic t.'s may be regarded as isomers and polymers of diisoprene,  $[ (CH_2)_2C=CH-CH_2 ]_n$  (cf. carotenoids, tocopherols); cyclic forms include menthane (cf. terpin), bornane, camphene. Terpenes containing 15, 20, 30, 40, etc., carbon atoms are called sesquiterpenes, diterpenes, triterpenes, tetraterpenes, etc.

**ter'phenyl** (*ter'-fe-ni'l*).  $C_6H_5-C_6H_4-C_6H_5$ , used as a scintillator in scintillation counting of radioactive decompositions.

**ter'pin**, Dipentenoediol;  $\rho$ -menthane-1,8-diol; a cyclic terpene alcohol,  $C_10H_{18}(OH)_2$ , obtained by the action of nitric acid and dilute sulfuric acid on pine oil.

**t. hydrate**, terpinol; a monohydrate of terpin; an expectorant.

**ter'pinol** (*ter-pin'-ol*).  $\rho$ -Menth-1-en-8-ol; an unsaturated aliphatic terpene obtained by heating terpin hydrate with dilute phosphoric acid; an active antiseptic and a perfume.

**ter'pinol**. Terpin hydrate.

**terra** (*ter'rah*) [ *L.* ]. Earth; soil.

**t. Japonica**, gambir.